REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 25, 27, 28, 30, and 31 are pending in this application. Claims 25, 27, 30, and 31 are amended; and claim 28 is hereby canceled without prejudice to pursuing the canceled subject matter in a continuing application. Applicant respectfully requests entry of the amendments and remarks made here into the file history of the application. Upon entry of these amendments, claims 25, 27, 30 and 31 will be pending and under active consideration.

b. Amendments to the Claims

Support for amended claims 25, 27, and 30 can be found in the application as originally filed as described in Table A.

Table A

Claim	Support
25	Table 1, lines 2838, 661199, and 624911-624912; Table 2A, lines: 423877-423973; Table 7A, lines 508069-508073; and paragraphs 0036, 0039, and 0046
27	Table 2A, lines 423877-423973; Table 7A, lines 508069-508073; and paragraphs 0036 and 0046-0050
30	Table 7A, lines 508094-508098; Table 8A, lines 1326486-1326511; and paragraphs 0036 and 0046

Claim 31 has been amended to no longer depend from canceled claim 28.

2. Patentability Remarks

a. 35 U.S.C. § 112, second paragraph

On pages 2-3 of the Office Action, the Examiner rejects claims 25, 27, 28, 30, and 31 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. The Examiner asserts that it is unclear what is meant by the limitation "RNA equivalent," and how and DNA can comprise at least 16 consecutive nucleotides of an RNA. The amended claims no longer recite the limitations "RNA equivalent" or "at least Y consecutive nucleotides… wherein Y is at least 16." Claim 28 is canceled, thereby rendering moot the rejection of this claim. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112.

b. 35 U.S.C. § 112, first paragraph

On pages 3-5, the Examiner rejects claims 25, 27, 28, 30, and 31 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner asserts that the specification does not contain clear, antecedent support for SEQ ID NO: 10,068,310. Applicant respectfully disagrees. Nevertheless, none of the amended claims recites this

SEQ ID NO. In view of these amendments, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

c. 35 U.S.C. §§ 101 and 112, first paragraph

On pages 5-11, the Examiner rejects claims 25, 27, 30, and 31 under 35 U.S.C. § 101 because the claimed subject matter is allegedly not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well established utility. In order to satisfy the utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as established in the art, and the utility must be credible. *See In re Fisher* 421 F.3d 1365, 1371 (2006) and *Revised Interim Utility Guideline Training Materials* ("Guidelines").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See In re Fisher* 421 F.3d at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a specific utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and *Guidelines*.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs were from a cDNA library of pooled leaf tissue isolated from a maize plant. The Fisher application did not disclose the location of the ESTs in the genome or the function of the underlying genes. Fisher asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) provide a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Id.* at 1367-1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids maybe used to target and modulate expression of **specific** gene transcripts. Table 2A, lines 423877-423973 and Table 7A, lines 508069-508073 of the application disclose that the claimed microRNA-related sequences specifically target mRNA transcripts of the MAPKAPK2 gene. Similarly, Table 7A,

lines 508094-508098 and Table 8A, lines 1326486-1326511 disclose that the newly claimed microRNA-related sequences of claim 28 specifically target mRNA transcripts of the SET gene. Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target genes MAPKAPK2 or SET**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating the MAPKAPK2 and SET genes.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. *See In re Fisher* at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a substantial utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and *Guidelines*.

In Fisher, it was admitted that the underlying genes for the ESTs had no known function. Fisher argued that this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, Fisher failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Id.* at 1373, quoting *Brenner v. Manson*, 383 U.S. 519 (1966).

In further sharp contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of MAPKAPK2[1] or SET.[2] At the time of filing, it was known in the art that MAPKAPK2 is a MAPK that is part of the p38 signaling pathway complex, a known substrate of p38 MAPK, and phosphorylates Ser^{473} of the serine/threonine-specific protein kinase family member Akt. *See* Taniyama Y *et al* (*Am J Physiol Cell Physiol* 2004;287:C494-9) ("Taniyama"). p38 mediates angiotensin II peptide hormone (ANG II)-induced vascular smooth muscle cell (VSMC) hypertrophy, which is mediated by Akt signaling. *Id.* ANG II induces MAPKAPK2-dependent phosphorylation of Akt, and this induction is inhibited *in vitro* by a specific peptide inhibitor of MAPKAPK2. *Id.* Accordingly, it was thought that MAPKAPK2 activity is critically important in VSMC hypertrophy, and that modulating MAPKAPK2 activity would be useful in therapeutic approaches to vascular remodeling in disease. *Id.*

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[1] *See* Table 7A, lines 508069-508073 and Table 8A, lines 1326174-1326203.

[2] *See* Table 7A, lines 508094-508098 and Table 8A, lines 1326486-1326511.

It was additionally known at the time of filing that SET[3] is a largely nuclear protein that modulates the activity of protein phosphatase 2A (PP2A). *See* Li M *et al* (*Jo Biol Chem* 1996;271(19):11059-62). PP2A is involved in tumorigenesis and the viral transformation of cells. *Id.* SET protein is a potent inhibitor of PP2A, and SET misexpression results in acute non-lymphocytic myeloid leukemia. *Id.* Further, SET is highly expressed in Wilms tumor formation. *See* Al-Murrani SWK *et al* (*Biochem J* 1999;341:293-8). Consistent with this effect, expressing SET in HEK-293 cells results in increased expression and phosphorylation of the c-Jun proto-oncogene. *Id.* Accordingly, SET expression could be modulated *in vitro* in cells to modulate PP2A and c-Jun activity and thereby modulate tumorigenesis.

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefits to the public. Such benefits are the ability to modulate the expression of MAPKAPK2 in order to modulate VSMC hypertrophy and remodel vasculature, and the ability to modulate the expression of SET to modulate PP2A and c-Jun activity in tumorigenesis. In view of the application providing particular targets of known function for the claimed microRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requirements are satisfied in accordance of Fisher and Guidelines.

(3) Credible Utility

An asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Accordingly, the invention must be operable to achieve useful results. *See Guidelines* at page 5 and *In re Swartz*, 232 F.3d 862 (Fed. Cir. 2000). The proper inquiry for determining credible utility is whether a person of ordinary skill in the art would conclude that the asserted utility is more likely than not true. Applicant respectfully submits that the record clearly shows that one of ordinary skill in the art would believe that the claimed nucleic acids may be used to modulate expression of the specific mRNA targets.

Dr. Yitzhak Pilpel, who is an expert in the field of microRNA and RNAi biology, states in the attached declaration (Appendix) that the claimed nucleic acids would likely inhibit expression of the MAPKAPK2 and SET mRNA transcripts. Dr. Pilpel's opinion is based on a number of facts.

(a) Characteristics of microRNA-target mRNA binding

Dr. Pilpel states that researchers in the microRNA field believed that there are a number of

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[3] SET is also known in the art as I_2^{PP2A}, putative class II human histocompatibility leukocyte-associated protein II (PHAP-II), and template activating factor-1β (TAF-1β).

characteristics of inhibition of protein expression via target mRNA interference by an endogenous or synthetic nucleic acid of 18-25 nucleotides in length, such as a microRNA. For example, the 5' end of the microRNA may contain a "seed" that is full complementary between the first 1-8 base pairs of the 5' of the microRNA and the target mRNA. *See* ¶¶ 2 and 3, Pilpel Declaration. This seed may be conserved and is often flanked by adenosine. *See* ¶ 3, Pilpel Declaration. If there is insufficient base-pairing of the microRNA 5' seed there may be compensatory complementation at the 3' end of a microRNA and its target mRNA sequence. *See* ¶ 3, Pilpel Declaration. Finally, although not obligatory, there may be multiple binding sites for a microRNA on a mRNA target, which may enhance the binding effect of target repression. *See* ¶ 3, Pilpel Declaration.

Importantly, Dr. Pilpel states that the claimed nucleic acid sequences as set forth in SEQ ID NOs: 7002375 and 7014085 and their respective target gene sequences of MAPKAPK2 (as depicted in column B, row 2, p. 5, Table A) and SET (column B, p. 6, Table A) are consistent with the characteristics of the microRNA:target mRNA binding described above. *See* ¶ 6, Pilpel Declaration. In view of these conserved characteristics, Dr. Pilpel concludes that the microRNAs of SEQ ID NOs: 7002375 (column B, row 2, p. 5, Table A) and 7014085 (column B, p. 6, Table A) are likely to inhibit expression of the protein encoded by the target genes MAPKAPK2 and SET, respectively, in view of the characteristics of microRNA:mRNA binding properties. *See* ¶ 6, Pilpel Declaration.

(b) MicroRNA algorithms

Dr. Pilpel states several effective microRNA:target algorithms have been based upon the characteristics of microRNA:target mRNA binding described above. *See* ¶ 4, Pilpel Declaration. Dr. Pilpel provides TargetScan (developed by Lewis *et al., Cell* 115:787-798 (2003)) and miRanda (developed by Enright *et al.*, *Genome Biology* 5:R1 (2003)) as examples of such algorithms. The TargetScan algorithm predicted 15 targets of various miRNAs identified by Lewis, and 11 of the predicted interactions between a particular miRNA and target mRNA were biologically validated with a false positive rate between 22 and 31%. The miRanda algorithm was also an effective microRNA:target algorithm, where 9 out of 10 predicted targets identified by the miRanda algorithm in Enright were biologically validated with a 24-39% false positive rate. *See* ¶ 4, Pilpel Declaration. MicroRNA:target interactions were also further validated by virtue of target binding site conservation among multiple organisms. *See* ¶ 5, Pilpel Declaration.

Importantly Dr. Pilpel states that SEQ ID NOs: 7002375 and 7014085 and their respective target gene sequences of MAPKAPK2 and SET are consistent with microRNA and target mRNAs predicted by the algorithms described above. *See* ¶¶ 4 and 5, Pilpel Declaration. Moreover, Dr. Pilpel states that the TargetScan algorithm detects the binding of SEQ ID NO: 7002375 (hsa-mir-494) to MAPKAPK2. *See* ¶ 5, Pilpel Declaration and row 2, page 5 of Table A. In view of these facts, Dr. Pilpel concludes that the

microRNAs of SEQ ID NOs: 7002375 and 7014085 are likely to inhibit expression of the respective proteins where co-expressed. *See* ¶ 6, Pilpel Declaration.

(c) MAPKAPK2 and SET

Applicant further submits that MAPKAPK2 and SET are credible targets for trans-acting regulatory elements. Specifically, the Pilpel Declaration indicates that the nucleic acid having the sequence as set forth in SEQ ID NO: 7002375 has been biologically validated, and its target binding site is conserved in at least two other organisms. *See* row 2, p. 5, Table A. Accordingly, MAPKAPK2 is an important target in nature by trans-acting elements such as microRNAs. Furthermore, the claimed nucleic acids are capable of binding MAPKAPK2 with 14 out of 22 nucleotides of complementarity, as demonstrated at Table 7A, lines 508069-508073 of the specification, and as shown below.

GAM NAME	GAM ORGANISM	GAM RNA SEQUENCE	TARGET BS-SEQ	TARGET	TARGET REF-ID	TARGET ORGANISM	UTR	BINDING-SITE DRAW (UPPER:GAM;LOWER:TARGET)	GAM POS
GAM353410	Human	ACATACAC GGGAAACC TCTTTT	AGGAGTGA GTGTATGT	MAPKAPK 2	NM_032960	Human	3	-- AGGAG TTCTC TT	- GA--- T A C AAGGG GTGTATGT CACATACA	A

The Pilpel Declaration also indicates that the nucleic acid having the sequence as set forth in SEQ ID NO: 7014085 is capable of binding SET with 13 out of 22 nucleotides of complementarity, as demonstrated at Table 7A, lines 508094-508098 of the specification, and as shown below.

GAM NAME	GAM ORGANISM	GAM RNA SEQUENCE	TARGET BS-SEQ	TARGET	TARGET REF-ID	TARGET ORGANISM	UTR	BINDING-SITE DRAW (UPPER:GAM;LOWER:TARGET)	GAM POS
GAM353410	Human	AAGGAGAG GTTGTCCG TGTTGT	AACATGGC TTCTCCTT	SET	NM_003011	Human	3	-- AACATGG TTGTGCC	C----T TCTCCTT AGAGGAA	B

In view of the foregoing, Applicant asserts that a person of ordinary skill in the art would more than likely conclude that the claimed nucleic acids may be used to modulate expression of MAPKAPK2 or SET, which in turn would respectively modulate VSMC hypertrophy and remodel vasculature, or modulate PP2A and c-Jun activity in tumorigenesis. Accordingly, a proper credible utility is asserted for the claimed nucleic acids. Applicant respectfully asserts that a specific and substantial utility has been demonstrated both in the specification and by what was recognized as well as established in the art at the time of filing, and the utility is credible. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 101.

d. 35 U.S.C. §112, first paragraph

On page 12 of the Office Action, the Examiner asserts that because the claimed subject matter lacks substantial utility, the specification also does not provide an enabling disclosure. Applicant disagrees. In view of the claimed subject matter having credible, specific, and substantial utility as described above, Applicant submits that the specification enables the claimed subject matter and

respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

e. 35 U.S.C. §102

In view of NEB Random Primer 24

On pages 12-14 of the Office Action, the Examiner rejects claims 25, 27, 28, and 30 under 35 U.S.C. § 102(b) as allegedly being anticipated by Random Primer 24, sold by New England Biolabs in the 1998/99 catalog ("NEB"). The Examiner asserts that NEB teaches a vial containing 9 copies of every possible 24-nucleotide sequence. The Examiner alleges that the specification contains no clear or limiting definition of the term "isolated" that would clearly preclude isolated mixtures of oligonucleotides of the type sold and disclosed by NEB. Applicant respectfully disagrees and submits that the Examiner's rejection is solely an issue of whether an "isolated" nucleic acid is taught by NEB.

The term "isolated" has a clear meaning to one of skill in the art. As the Examiner notes on page 13, NEB teaches a vial containing over 2.81×10^{14} possible 24-nucleotide sequences. Even if one such tube contained a nucleic acid with the sequence of the claimed nucleic acid, NEB teaches this nucleic acid as only one among 2.81×10^{14} nucleic acids in the vial. One sequence among 2.81×10^{14} is not an isolated nucleic acid. Accordingly, NEB does not specifically teach the sequences of the instantly claimed nucleic acids.

Finally, amended claims 25 and 30 are related to sequences of 22 nucleotides in length, and amended claim 27 is related to a sequence of 81 nucleotides. Accordingly, NEB teaches only 24-mers and does not disclose the claimed nucleic acids, and therefore does not teach all the limitations of amended claims 25, 28, or 30. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102(b) in view of NEB.

In view of US 6,582,908

On pages 14 and 15 of the Office Action, the Examiner rejects claims 25, 27, 28, and 30 under 35 U.S.C. § 102(b) as allegedly being anticipated by Fodor *et al* (U.S. Pat. No. 6,582,908; "Fodor"). The Examiner asserts that Fodor teaches a nucleic acid array comprising all possible 20-mers, thereby anticipating DNA equivalents of the instantly claimed nucleic acids. Applicant respectfully disagrees.

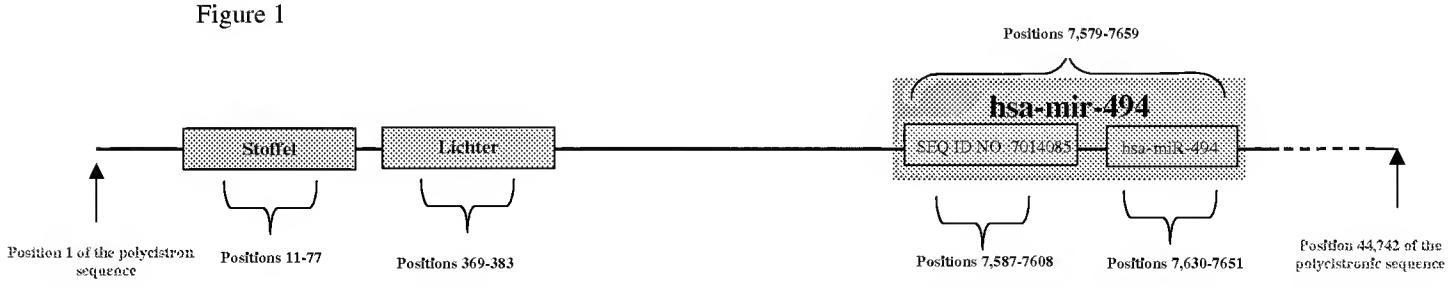
As discussed above, amended claims 25, 27, and 30 are directed to isolated nucleic acids. The array of Fodor cited by the Examiner comprises nearly 1.1×10^{12} different sequences. One sequence among 1.1×10^{12} is not isolated. Accordingly, Fodor does not teach all the limitations of amended claims 25, 27, or 30. Claim 28 is canceled, thereby rendering moot the rejection of this claim. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102(b) in view of Fodor.

In view of US 6,432,639 and in view of US 20050227934

On pages 15 and 16 of the Office Action, the Examiner rejects claims 25 and 28 under 35 U.S.C. § 102(b) as allegedly being anticipated by Lichter *et al* (U.S. Pat. No. 6,432,639; "Lichter"). Applicant respectfully disagrees. Lichter teaches a sequence with SEQ ID NO: 27 that allegedly aligns with a sequence corresponding to positions 369 to 383 of SEQ ID NO: 10068310. Amended claim 25 is related to a sequence corresponding to positions 7630-7651 of SEQ ID NO: 10068310; amended claim 27 is related to a sequence corresponding to positions 7579-7659 of SEQ ID NO: 10068310; and amended claim 30 is related to a sequence corresponding to positions 7587-7608 of SEQ ID NO: 10068310. As shown in Figure 1, the Lichter sequence is not related to a sequence corresponding to any of the three foregoing positions within SEQ ID NO: 10068310.

Additionally, on pages 16 and 17 of the Office Action, the Examiner rejects claims 25, 28, and 31 under 35 U.S.C. § 102(e) as allegedly being anticipated by Stoffel *et al* (U.S. Pat. Pub. No. 2005/0227934 A1; "Stoffel"). Applicant respectfully disagrees. Stoffel teaches a sequence with SEQ ID NO: 25 that allegedly aligns with a sequence corresponding to positions 11-77 of SEQ ID NO: 10068310. As discussed above, amended claim 25 is related to a sequence corresponding to positions 7630-7651 of SEQ ID NO: 10068310; amended claim 27 is related to a sequence corresponding to positions 7579-7659 of SEQ ID NO: 10068310; and amended claim 30 is related to a sequence corresponding to positions 7587-7608 of SEQ ID NO: 10068310. As shown in Figure 1, the Stoffel sequence is not related to a sequence corresponding to any of the three foregoing positions within SEQ ID NO: 10068310.

Figure 1



Accordingly, neither Lichter nor Stoffel teaches SEQ ID NOs: 7002375, 6816665, or 7014085, and therefore do not teach all the limitations of amended claims 25, 27, or 30. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102(b) in view of Lichter and in view of Stoffel.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone

conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: March 20, 2008

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